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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,724	03/06/2002	Samy Ashkar	CMCC 820	6946
9629	7590	01/26/2006	EXAMINER	
MORGAN LEWIS & BOCKIUS LLP 1111 PENNSYLVANIA AVENUE NW WASHINGTON, DC 20004			MYERS, CARLA J	
			ART UNIT	PAPER NUMBER
			1634	
DATE MAILED: 01/26/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center">Advisory Action Before the Filing of an Appeal Brief</p>	Application No. 10/091,724	Applicant(s) ASHKAR, SAMY	
	Examiner Carla Myers	Art Unit 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 January 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 05 January 2006. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
- The status of the claim(s) is (or will be) as follows:
- Claim(s) allowed: _____.
- Claim(s) objected to: _____.
- Claim(s) rejected: 1-18 and 23.
- Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

ATTACHMENT TO ADVISORY:

In the after final response filed January 5, 2006, Applicants traversed the previous rejections under 35 U.S.C 103. IN SUMMARY, the traversal is on the grounds that Clark-Curtis does not teach that protein stability is better in minicells. This argument is unclear since the rejection does not state that protein stability is greater in all minicells. The rejection states that Clark-Curtiss teaches the use of minicells in which protein stability is greater. Further, there is no requirement for the reference to teach that protein stability is greater in all minicells. Applicants point to the teachings of Chung and Mizusawa as evidence that the minicells of Clark-Curtiss contain a lon mutation and that minicells containing the lon mutation have a decreased ability to degrade abnormal proteins. The teachings of Chung and Mizusawa have been fully considered. Again, it is agreed that Clark-Curtiss teaches minicells having a lon mutation and that Clark-Curtiss teaches that these minicells provide the advantage that foreign proteins expressed by the minicells will be less likely to be subjected to proteolysis.

Applicants state that one would not have been motivated to have combined the teachings of Clark-Curtiss with the teachings of Huang because the minicell, independent of the mutations responsible for decreased capacity to degrade proteins, confers greater protein stability than a bacterial cell. This argument has been fully considered but is not persuasive. It is maintained that the ordinary artisan would have in fact been motivated to have used the minicells of Clark-Curtiss in the method of Huang in order to have expressly achieved the benefits set forth by Clark-Curtiss that these minicells would have provided a means for producing proteins in a system in which

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protein stability would not be compromised. As previously indicated, Clark-Curtiss states that "(p)rotein products produced by recombinant molecules are often unstable in *E. coli* owing to proteolytic degradation. Mutant derivatives of mini-cell producing strains that have *lon* (*capR*, *deg*) mutations are often quite useful in such instance. When the "foreign" genetic information expressed in *E. coli* complements the gene defect in the minicell-producing strain, we have frequently isolated spontaneous mutants for their better growth under conditions that select for maximal expression of the genetic information. Very often these mutants will possess mutations in the *lon* locus, which decreases the rate or extent of proteolytic degradation of "foreign" gene products" (page 351). Thereby, Clark-Curtiss does teach that minicell strains having *lon* mutations or other mutations are advantageous in that they allow for the synthesis of proteins having greater stability. It is again noted that the present claims encompass the use of any type of minicell, including the minicells of Clark-Curtiss having a *lon* mutation.

Applicants state that no evidence has been provided from either reference to show that the advantage achieved using minicells is related to the lack of chromosomal DNA in minicells. Applicants cite *In re Millis* for the finding that the mere fact that references can be combined does not render the combination obvious. However, it is maintained that Clark-Curtiss (page 347) does in fact teach that minicells contain protein but "little or no chromosomal DNA." Further, it is maintained that the ordinary artisan would have recognized that synthesis of the fusion protein in minicells would have enhanced the specificity of the detection of the fusion protein because minicells are not subject to the high background of chromosomal gene products which occurs

when using bacterial cells. Additionally, Applicant's argument is not convincing because for the purposes of combining references, those references need not explicitly suggest combining teachings much less specific references, In re Nilseen, 851 F. 2d 1401, 7 USPQ2d 1500 (Fed Cir. 1988). As stated in Ex parte Levengood, 28 USPQ2d 1300, "In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention". Indeed, motivation for combining the teachings of the various references need not be explicitly found in the references themselves, but may be provided by the examiner based on logic and sound scientific reasoning. In the present situation, those of ordinary skill in the art would have clearly recognized the benefits of using a cell that contained little or no interfering chromosomal DNA in a method for detecting the expression of a specific heterologous protein. Applicants have not provided any evidence or sound scientific arguments to contradict this finding.

Lastly, Applicants arguments regarding long-felt need are not persuasive. It is first noted that the assertion of long-felt need was not presented earlier. Further, the licensing of the minicell technology to Sopherion Therapeutics was not previously addressed, nor have the details of this licensing agreement been disclosed. To establish the long-felt of an invention first requires providing objective evidence that the art recognized the problem for a long period of time without a solution. Additionally, the

long felt need must not have been satisfied by another (in the same or different manner) before the invention by Applicant. Third, the invention must in fact satisfy the specifics of the long-felt need and the claimed invention must be directed to the subject matter of the long-felt need. In the present situation, Applicants have not provided evidence to fulfill each of these requirements. Applicants assert that the bacterial display systems and minicells have been in use for 20 years, but that no one had put the two together to achieve a more effective and robust screening method. However, in the art of detection assays there is always a need to improve the effectiveness and efficiency of detection and therefore such a desire to improve the effectiveness and efficiency is not considered to be a long felt need. Further, the evidence of record does not establish that other attempts to solve the problem or need have been made but were unsuccessful. Applicants cite a bacterial expression system which is characterized as limited in its ability to display proteins of large sizes. However, the claims are not limited to the expression of fusion proteins of any particular size. Additionally, no evidence has been provided to show that persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. Applicants attention is directed to MPEP § 716.04, which sets forth the requirements for establishing long-felt need and the failure of others to achieve this need.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

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The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
January 24, 2006


CARLA J. MYERS
PRIMARY EXAMINER